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Visible Light-Mediated C–H Alkylation of Pyridine Derivatives

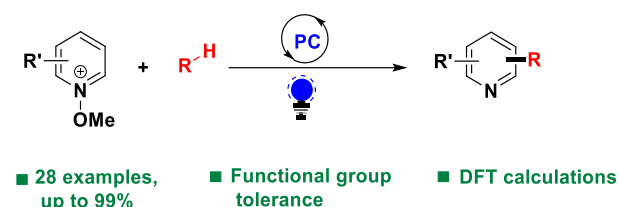
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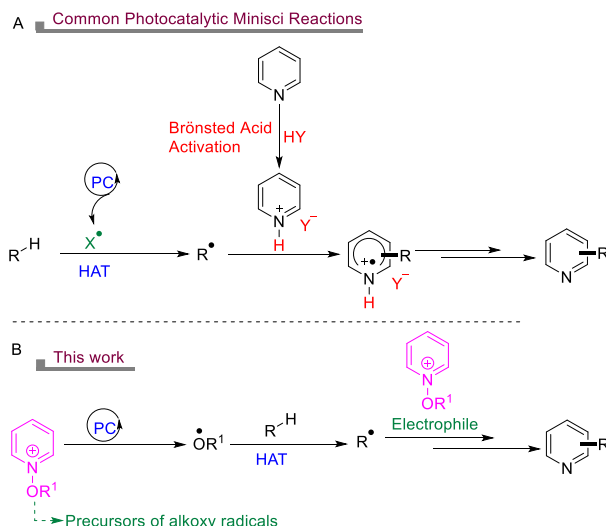
Supporting Information Placeholder



ABSTRACT: We report herein a visible light-mediated C–H alkylation of pyridine derivatives that proceeds by simple combination of a large variety of N-alkoxy-pyridinium ions with alkanes in the presence of 2 mol% of fac-Ir(ppy)₃ under blue illumination. The mild reaction conditions together with the high group functional tolerance make of this process a useful synthetic platform for the construction of structurally strained heterocycles. Detailed mechanistic investigations, including Density Functional Theory (DFT) calculations and quantum yield measurement, allowed to understand factors controlling the reactivity and the selectivity of the reaction.

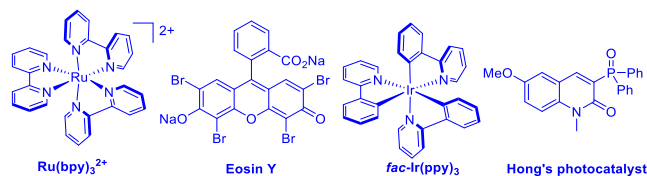
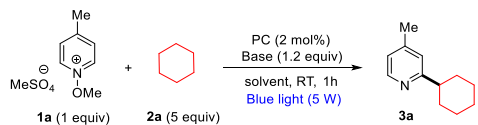
Alkylated heteroarenes are ubiquitous chemical motifs present in pharmaceuticals, natural products, and ligand scaffolds.^{1,2} While access to such molecules can be achieved with different synthetic methodologies, the oxidative cross-coupling between two C–H compounds is evidently one of the most elegant approaches as it provides a direct construction of the C–C bond in a step- and atom-economical fashion.^{3–7} For instance, the generation of an alkyl radical through a hydrogen atom transfer (HAT) event and its subsequent addition to a heteroarene ring followed by a formal hydrogen atom loss can provide a rapid and direct method for heterocycle C–H alkylation. This approach, known as the Minisci reaction,^{8–11} gained much attention during the last decade with the spectacular renaissance of the field of photoredox catalysis that provides very mild conditions for the generation of alkyl radicals.^{12–19} While various elegant photoredox Minisci reactions employing HAT strategy for the generation of the alkyl radical have been developed, there is in most cases need to use an external oxidant and stoichiometric amounts of Brønsted acids to activate the heteroarene ring towards radical addition.^{20–27}

Scheme 1. (A) Reported Approaches for C–H Alkylation of Heteroarenes. (B) Current work. HAT denotes Hydrogen Atom Transfer.



Based on their abilities to generate strong hydrogen atom abstractors (alkoxy radicals) under visible light photocatalytic conditions,^{28,29} as well as their high electrophilicity, *N*-alkoxypyridinium ions (NAPs) are unique scaffolds to achieve photocatalytic Minisci reaction. This approach has nicely been demonstrated by the Hong group in a certain number of examples, including acylation and intramolecular alkylations.³⁰⁻³⁴ However, the direct association of NAPs with alkanes to achieve Minisci reaction has not been reported so far. Furthermore, it is well known that pyridines are less reactive than quinolines and isoquinolines in various Minisci reactions.³⁵⁻³⁷ We therefore decided to investigate the reactions of NAPs with alkanes under mild photoredox conditions.

Table 1. Optimization of the Photocatalytic Alkylation Reaction between the *N*-alkoxypyridinium 1a and Cyclohexane 2a.^a



entry ^a	photocatalyst (PC)	base	solvent	3a, yield [%] ^b
1	Ru(bpy) ₃	NaHCO ₃	MeCN	traces
2	Eosin Y	NaHCO ₃	MeCN	traces
3	Hong's PC	NaHCO ₃	MeCN	64
4	<i>fac</i> -Ir(ppy) ₃	NaHCO ₃	MeCN	95
5	<i>fac</i> -Ir(ppy) ₃	NaHCO ₃	THF	traces
6	<i>fac</i> -Ir(ppy) ₃	NaHCO ₃	DMF	traces
7	<i>fac</i> -Ir(ppy) ₃	NaHCO ₃	DCM	traces
8	<i>fac</i> -Ir(ppy) ₃	NaHCO ₃	AcOEt	traces
9	<i>fac</i> -Ir(ppy) ₃	NaHCO ₃	DMSO	traces
10	<i>fac</i> -Ir(ppy) ₃	NaHCO ₃	CHCl ₃	traces
11	<i>fac</i> -Ir(ppy) ₃	Na ₂ CO ₃	MeCN	30
12	<i>fac</i> -Ir(ppy) ₃	K ₂ HPO ₄	MeCN	55

13	<i>fac</i> -Ir(ppy) ₃	K ₂ CO ₃	MeCN	41
14	-	NaHCO ₃	MeCN	traces
15	<i>fac</i> -Ir(ppy) ₃ ^c	NaHCO ₃	MeCN	0
16	<i>fac</i> -Ir(ppy) ₃	-	MeCN	33

^a Reaction conditions: *N*-methoxy-4-methylpyridinium methyl sulfate **1a** (0.21 mmol, 1 equiv), cyclohexane **2a** (1.1 mmol, 5 equiv), solvent (4.2 mL), blue LEDs (5W), 1 h. ^b NMR yields are determined from ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as internal standard. ^c reaction performed in the dark.

We initially explored the reaction conditions by investigating the effect of the photocatalyst, solvent, and the base through the reaction of the *N*-methoxy-4-methylpyridinium (**1a**) with **2a**. As shown in Table 1, *fac*-Ir(ppy)₃ gave excellent conversion of **3a** (Table 1, entry 4, 95%) when 5 equivalents of **2a** were mixed with **1a** in the presence of NaHCO₃ as a base in acetonitrile under blue light irradiation. While good conversion was obtained with the 3-phosphonated quinolinone (entry 3, 64%), known as the Hong photocatalyst, under the same conditions as with *fac*-Ir(ppy)₃, only traces of **3a** were observed with Ru(bpy)₃ and Eosin Y (entries 1 and 2). A solvent screening, including THF, DMF, DCM, AcOEt, DMSO, and CH₃Cl (entries 5-10) revealed no formation of the desired adduct. We next studied the effect of the base on the reaction and found modest conversion (30-55%) with the inorganic bases Na₂CO₃ (entry 11), K₂HPO₄ (entry 12) and K₂CO₃ (entry 13). The absence of photocatalyst (entry 14) and the visible-light irradiation (entry 15) were detrimental for the C-H alkylation as no product has been observed. Finally, 33% of **3a** was observed when the base was not employed under the optimized conditions (entry 16). The result might be attributed to the pyridinium counterion that played the role of the base in the process.

Next, we set out to investigate the scope of this visible-light C-H alkylation of heteroarenes with alkanes (Figure 1). The reaction of cyclohexane (**2a**) with 4-substituted *N*-alkoxy-4-methylpyridinium ions proceeded smoothly, giving the 2-alkylated pyridines (**3a-3f**) in 50-99% yields. Remarkably, the reaction works well with both electron-donating or electron-withdrawing groups, tolerating cyano (**3c**), trifluoromethyl (**3d**) and carbonyl (**3e**) groups.

The reaction works equally well with 2-substituted pyridiniums. Both regioisomers C2- and C4-alkylated pyridines (**3g-3j**) were obtained in equal proportion (1:1 ratio), except in the case of 2-benzylpyridinium ion where the C2 adduct was obtained as a major regioisomer (C2:C4 = 4:1). The reaction is not only restricted to pyridines as alkylated quinolines (**3k-3n**), 2,2-quinoline (**3o**) and phenanthridine (**3p**) were obtained in good to excellent yields (Figure 1).

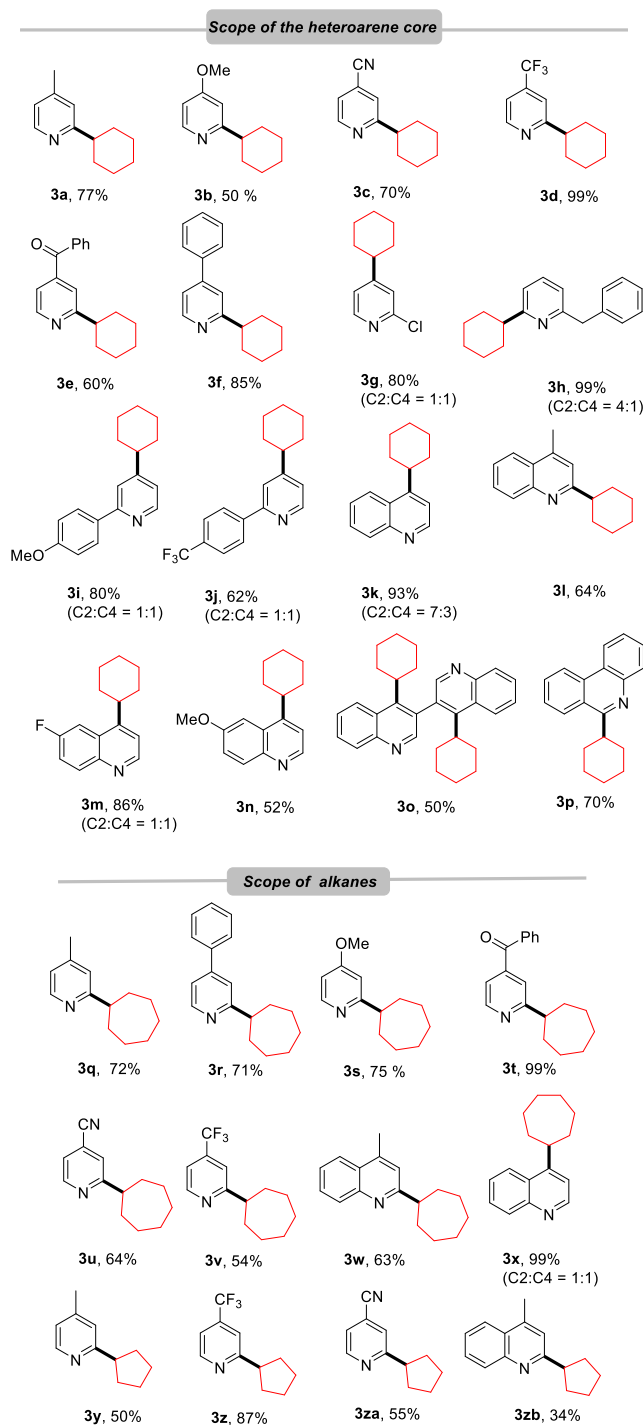


Figure 1. Photocatalytic C–H Alkylation of Heteroarenes.^a

^a Reaction conditions: *N*-alkoxyppyridinium methylsulfate **1** (1 equiv), **2a** (5 equiv), *fac*-Ir(ppy)₃ (2 mol%), NaHCO₃ (1.2 equiv) CH₃CN (0.05 M), blue LEDs (5W), 1 h.

We further extend the scope of the photocatalytic approach to cycloheptane (**2b**) and cyclopentane (**2c**) (Figure 2). Remarkably, a large variety of heteroarylated-alkanes (**3q–3zb**) were isolated in yields going from 34 to 99%. Here again, the reaction is compatible with quinolines derivatives.

The reaction mechanism of the visible-light-mediated alkylation of heteroarenes is depicted in Figure 2. It starts with the generation of the methoxyl radical through single-electron reduction of the *N*-alkoxyppyridinium ion by the excited state of the photocatalyst (PC*). This event is thermodynamically viable and we have previously demonstrated the generation of (MeO•) by EPR spectroscopy.^{38,39,40,41} DFT calculations show plausible HAT between the methoxyl radical and cyclohexane (**2a**) to form the cyclohexyl radical (**Int 1**). The latter reacts at the

C4 of the pyridinium ion (**1**) position ($\Delta G^\ddagger = 14.4$ kcal/mol) to form the radical intermediate (**Int2**). The radical addition at the C2 position proceeds with an activation energy of 14.8 kcal/mol. This weak difference between both attacks, *i.e.* at C2 and C4 position, may rationalize the low regioselectivity observed. Next, a fast deprotonation of **Int2** by a base gives the **Int3** that upon N–O bond cleavage forms the final product **3** and release the methoxyl radical to start a new reaction cycle. This radical chain pathway explains the high measured quantum yield of the reaction $\Phi = 62.9$ (see Supporting Information for details). The calculated mechanism is in good agreement with the experimental reaction time.

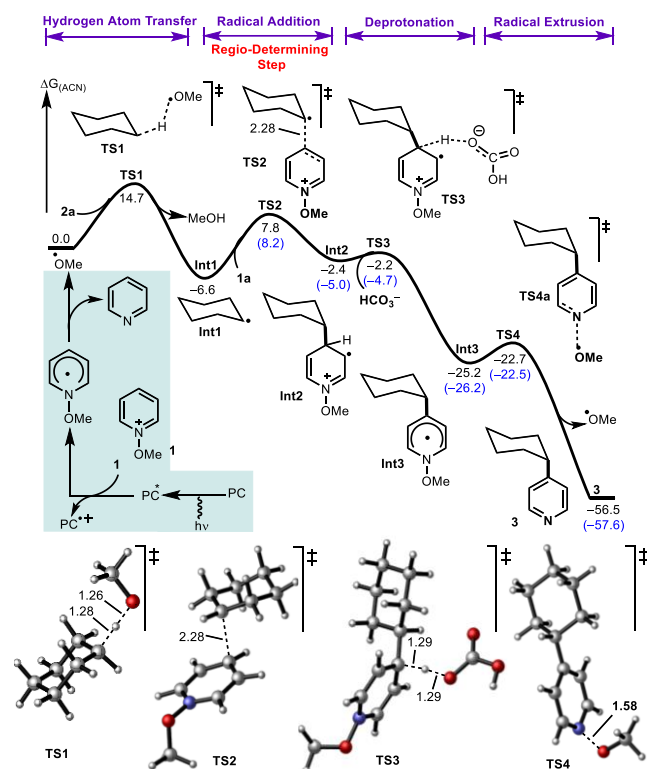


Figure 2. Free energy profile for the photoinitiated C–C bond formation in the reaction of pyridinium ion and cyclohexane. Calculations were performed at the SMD-(ACN)-M06-2X/def2-TZVP//B3LYP/6-31+G(d) level of theory. Energies between brackets are reported for the addition at C2-position. See Supporting Information for computational details.

Although visible-light-mediated alkylation of heteroarenes has widely been reported during the last few years, the reaction scope has mainly been restricted to isoquinolines, quinolines. In this study, we showed that alkylation of pyridines can also be achieved efficiently by simply combining *N*-methoxypyridinium ions with alkanes in the presence of low loading (2 mol %) of the readily accessible *fac*-Ir(ppy)₃ under blue light illumination. The broad scope and functional group tolerance are excellent features of this method. The detailed experimental and computational mechanistic studies conducted in this study are not only allowed understanding factors controlling this photoalkylation reaction but will also help the design of new visible light-induced C–H functionalization of heteroarenes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Quantum yield measurement, DFT calculations, experimental procedures, characterization data, and NMR spectra

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DEDICATION

This work is dedicated to Prof. Pierre. H. Dixneuf (University of Rennes) for his excellent contribution to organometallic chemistry and catalysis.

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